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Relapsing *Aspergillus* otomycosis despite prolonged systemic antifungal therapy and resolution after topical voriconazole administration: A case report

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ABSTRACT

We report a case of intractable *Aspergillus* otomycosis with multiple relapses despite conventional topical and systemic antifungal treatment, and adjunctive usage of hyperbaric oxygen therapy. Of note, otomycosis relapsed even after six months of continuous systemic antifungal treatment with therapeutic drug levels and without treatment interruption; and only resolved after application of topical voriconazole. (max. 75 words)

1. Introduction

Otomycosis is commonly encountered in clinical practice; however, its management can be challenging because of a high recurrence rate and limited therapeutic options. *Aspergillus* is the most frequently isolated fungi in patients with otomycosis [1]. Otomycosis is treated via intensive debridement and cleansing, and application of topical antifungals; in cases refractory to topical treatment, or where deeper invasion has occurred, systemic antifungals can be utilised [2–4]. Oral triazole drugs, such as voriconazole, posaconazole and isavuconazole, have coverage against mould infections, including *Aspergillus*, and have reasonable penetration of bone and the central nervous system [2]. While favourable outcomes have been reported in the literature with usage of oral voriconazole for *Aspergillus* otomycosis [3,4], systemic antifungal treatment is often utilised only after topical therapy has failed, due to concerns of tolerability and side effects. Topical voriconazole has been utilised in case reports as an alternative option for treating refractory otomycosis failing to respond to usual therapeutic options [5,6]; though otic administration of topical voriconazole is not a conventional mode of drug delivery, and at present is not licensed for such use [7]. We report a case of intractable *Aspergillus* otomycosis with multiple relapses despite conventional topical and systemic antifungal treatment, and adjunctive usage of hyperbaric oxygen therapy. Of note, otomycosis relapsed even after six months of continuous systemic antifungal treatment with therapeutic drug levels and without treatment interruption; and only resolved after off-label application of topical voriconazole.

2. Case presentation

The patient was an elderly (≥80 years) female with no history of systemic immunocompromise; she had a history of right mastoidectomy 20 years prior for cholesteatoma. During routine surveillance of her mastoid bowl, it had always been clean and dry. She presented with a history of yellowish otorrhea for one week. On otoscopy, whitish debris was visualised in the right ear canal with blackish structures; the tympanic membrane was intact. She was initially treated with topical clotrimazole and repeated weekly aural toilet for two months; however, otalgia worsened, otorrhea persisted and pus was recurrently visualised, with recurrence of fungal structures. The ear swab specimens were inoculated onto Sabouraud Dextrose Agar (SDA) and Sabouraud Dextrose Agar with chloramphenicol (SDC) agar slants, and incubated at 30° Celsius at ambient atmosphere for 4 weeks. Ear fungal cultures at D1 grew *Aspergillus niger* complex (Fig. 1A); bacterial cultures were

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negative. Computed-tomography (CT) scan of the temporal bone showed right otitis externa with thickening and enhancement of the auricle and cartilaginous external auditory canal. There was no bony involvement to prove malignant otitis externa. Topical therapy was switched to gentian violet and in light of fungal persistence, the patient was referred to infectious diseases for consideration of systemic antifungals. Antifungal susceptibility showed minimal-inhibitory-concentrations (MICs) of 0.06 μg/ml for posaconazole; 0.50 μg/ml for voriconazole; and 0.19 μg/ml for isavuconazole. Isavuconazole was tested using MIC Test Strip (Liofilchem^{R}), while the other drugs were tested using Sensititre™ YeastOne™ YO10 AST Plate (Thermo Scientific). She was initially started on oral voriconazole 200 mg BD for a week; however, she could not tolerate oral voriconazole due to visual disturbances and hence therapy was switched to oral isavuconazole 200 mg once-daily. She completed six weeks of oral isavuconazole with good interval resolution of symptoms. At D90 (six weeks after cessation of antifungals), she again complained of recurrent otorrhea and fungal structures were again seen; ear cultures again grew *Aspergillus niger* complex. Antifungal susceptibility testing was again repeated, which showed MICs of 0.03 μg/ml for posaconazole; 0.50 μg/ml for voriconazole; and 0.19 μg/ml for isavuconazole. The patient was restarted on oral isavuconazole again during the first relapse; topical clotrimazole and other topical agents such as gentian violet and acetic acid were again resumed, together with regular aural toilet. There was initial treatment response; however at D204 (114 days of isavuconazole), the patient again complained of right otalgia and fungal structures were again visualised in the right external auditory canal. *Aspergillus niger* complex was again isolated; antifungal susceptibility testing was again repeated, which again showed consistent sensitivity to azoles (MICs of 0.06 μg/ml for posaconazole; 0.50 μg/ml for voriconazole; and 0.094 μg/ml for isavuconazole). Given persistent isolation of the same pathogen with similar susceptibilities, we felt that this represented recurrent infection, though re-infection could not be fully excluded. Given that her infection recurred despite being on systemic antifungals, the patient was switched over to oral posaconazole at a dose of 150 mg once-daily during her second relapse, with the intention to perform therapeutic-drug-monitoring of posaconazole trough levels to preclude the possibility of treatment failure due to inadequate serum concentrations of the drug. Blood posaconazole trough levels taken prior to administration of the next dose were within acceptable ranges (>1.0 mg/L). Magnetic-resonance-imaging (MRI) showed an area of enhancement along the posterior aspect of the right mastoidectomy bowl, with no associated restricted diffusion (Fig. 1B). Topical gentian violet and clotrimazole was continued; during her second relapse, she also received a course of hyperbaric oxygen therapy (HBOT) over 40 sessions. Despite treatment, however, ear discharge recurred at D304 (100 days of posaconazole therapy), and ear cultures again grew *Aspergillus niger* complex. Repeated antifungal susceptibility testing again showed consistent sensitivity to azoles (MICs of 0.06 μg/ml for posaconazole; 0.50 μg/ml for voriconazole; and 0.125 μg/ml for isavuconazole). MRI-scan was repeated, which showed a stable area of enhancement along the posterior aspect of the right mastoidectomy bowl. At this point, the patient had had three relapses of *Aspergillus* otomycosis; despite being on systemic antifungal treatment for more than six months continuously, with therapeutic serum levels of posaconazole. Given recurrent relapses, topical 1% voriconazole eyedrops were adapted for otic use, with administration of three drops three-times-a-day. Topical 1% voriconazole was continued for eight weeks with good interval resolution and no side effects; blood voriconazole levels were undetectable. The patient was followed-up for six months without relapse.

3. Discussion

While topical voriconazole has been utilised in occasional case reports for the treatment of refractory *Aspergillus* otomycosis [5,6], to the best of our knowledge, this is the first report of topical voriconazole succeeding in eradication of otomycosis where systemic triazole antifungals have failed. In previous cases, topical voriconazole was utilised after failure of repeated treatments with other topical antifungals (eg. nystatin, clotrimazole) [5,6]; systemic triazoles were not utilised due to concern regarding tolerability and side effects. Our patient could not tolerate systemic voriconazole due to side-effects, and alternative systemic triazoles (posaconazole, isavuconazole) were utilised instead. *In-vitro* antifungal susceptibility testing showed low MIC values of the

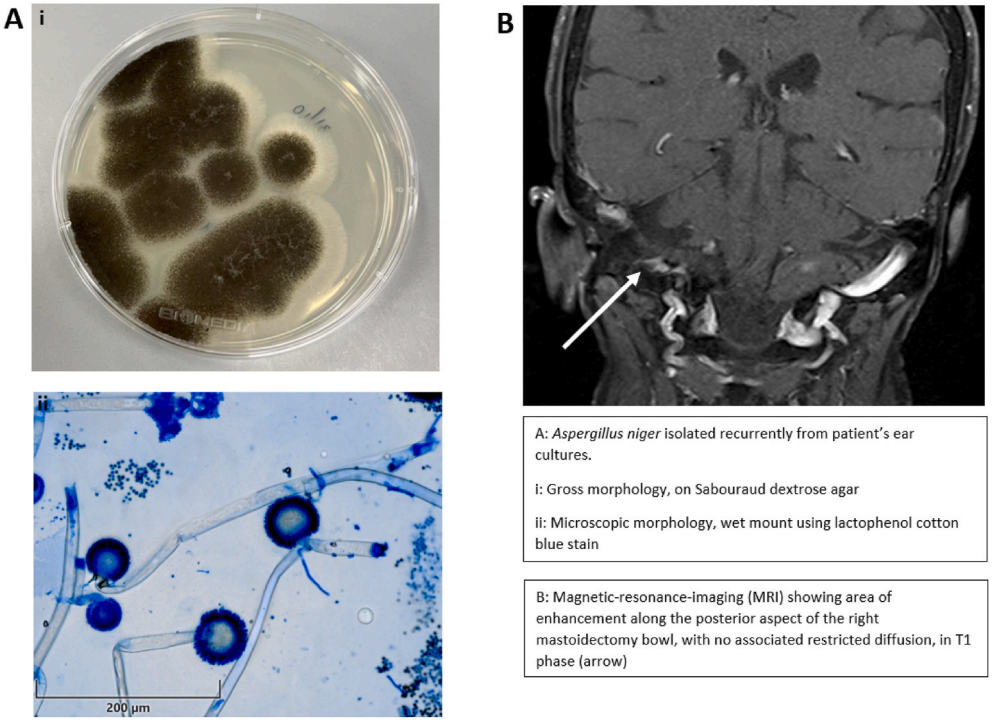

Fig. 1. Relapsing *Aspergillus niger* otomycosis refractory to systemic azoles: microbiology results and radiological features.

Aspergillus isolates to these antifungals. However, relapse of otomycosis occurred even while our patient was on systemic antifungals without treatment interruption and adequate blood posaconazole levels. In contrast, elsewhere in the literature where systemic triazoles (eg. voriconazole) was utilised in the management of refractory *Aspergillus* otomycosis, recurrences were noted only infrequently and only after treatment cessation; no cases of relapse were reported while treatment was still maintained [3,4]. Topical administration of voriconazole via unconventional methods (i.e. otic usage of a voriconazole sterile solution previously validated for treatment of eye infections) potentially increased drug concentration at the infection site, allowing for successful eradication where systemic antifungal therapy failed. Biofilm formation has been implicated in cases of *Aspergillus* otomycosis as a potential contributory factor to relapse [8]; it remains to be seen if administration of topical antifungals may allow for better biofilm penetration and thereby contribute to eradication. Additionally, usage of topical voriconazole minimised toxicities and/or drug interactions associated with conventional (systemic) administration. Blood voriconazole levels were undetectable in our patient, indicating lack of systemic absorption after topical administration, and the patient did not experience the same side effects (visual disturbances) earlier experienced with oral voriconazole. Hyperbaric oxygen therapy was utilised as adjunctive treatment for refractory otomycosis given case reports of successful use in malignant otits externa [9,10]; however, in our case, relapse occurred despite use of hyperbaric oxygen. We demonstrate that topical voriconazole can be used successfully and safely for eradication of *Aspergillus* otomycosis refractory to local treatment, other topical agents, and even, in this case, where relapse occurred even during concurrent administration of systemic antifungals.

Ethical form

Ethics approval was not required for case reports under our institutional review board guidelines. Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Declaration of competing interest

There are no conflicts of interest.

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